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# LETTER TO THE EDITOR

## Glucocorticoid Use and Melanoma Risk

Maria Teresa LANDI[1]*, Andrea BACCARELLI,[1,2] Donato CALISTA,[3] Thomas R. FEARS[4] and Giorgio LANDI[3]

[1]*Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, NCI, Bethesda, MD, USA*
[2]*EPOCA, Epidemiology Research Center, University of Milan, Milan, Italy*
[3]*Dermatology Unit, Bufalini Hospital, Cesena, Italy*
[4]*Biostatistic Branch, National Cancer Institute, Bethesda, MD, USA*

*Dear Sir,*

Glucocorticoids (GC) have been shown to inhibit *in vitro* growth of human and murine malignant melanoma cells[1–5] and to reduce melanoma tumor progression in animal experiments.[6–8] *In vitro* and animal studies showed that dexamethasone inhibits synthesis of pro-opiomelanocortin (POMC) and MSH peptides,[9,10] which are presumed to induce melanocyte cell proliferation.[11] Subjects with primary cortisol deficiency constantly exhibit increased POMC. Diffuse epidermal and mucosal hypermelanosis[12] and eruptive nevi[13] have been described in such patients. Glucocorticoid receptors are widely expressed in normal and transformed melanocytes, as well as in other epithelial cells.[14] Glucocorticoid receptor loss in metastatic B16BL6 murine melanoma is accompanied by an increasing proliferation rate.[15] However, the effect of GC on melanoma development is controversial.[16,17] Recent reports have not addressed the effect of GC administration on melanoma progression in humans, although earlier studies showed mixed results.[18,19]

We conducted a case-control study of risk factors for cutaneous malignant melanoma (CMM) at the Maurizio Bufalini Hospital in Cesena, Italy, from December 1994 to January 1999. The Bufalini Hospital's Ethical Committee approved the study. One hundred eighty-three newly diagnosed incident CMM cases of any stage (87 males and 96 females) and 179 (89 males and 90 females) controls agreed to participate and signed an informed consent. Response rate was approximately 95% for cases and 83% for controls. Controls were identified at the time of case collection among spouses or close friends of the cancer cases (134), among outpatients referred to the hospital due to small accidental trauma (14) and among healthy volunteers from the Bufalini Hospital personnel (31). All controls were from the same geographic area of the cases and were frequency-matched to cases by age and gender.

A pilot-tested questionnaire was administered to all subjects by personal interview. Among questions on medical history and personal characteristics, subjects were asked whether they had any GC therapy during the previous 5 years. Two cases and 3 controls were excluded from the analysis because of nonresponse. Therapy brands, treatment type (topical *vs.* systemic), length of treatment and reason for the therapy were collected. We calculated odds ratios (OR), 95% confidence intervals (CI) and tests for trend for the association between GC use and melanoma risk by multiple logistic regression analysis. Logistic regression was unconditional but included terms for the matching variables, *i.e.,* age and gender, in addition to the strongest risk factors for melanoma, such as skin color, eye color, tanning ability and presence of dysplastic nevi, selected through stepwise regression analyses (criteria for entry in the model: $p < 0.05$ to $p > 0.10$). GC use was not associated with these factors ($p \geq 0.19$) in control subjects. Similarly, no association was found between GC use and gender ($p = 0.86$) or age ($p = 0.16$).

GC use showed a protective effect against CMM risk (subjects who had GC therapy included 25 cases and 44 controls, OR = 0.39, 95% CI = 0.20–0.74). The association was statistically significant ($p = 0.004$). A negative trend ($p = 0.008$) in CMM risk was found with duration of GC treatment. Eighteen cases and 26 controls had GC therapy for less than 2 months, while 6 cases and 12 controls were treated for more than 2 months (OR = 0.44, 95% CI = 0.21–0.94 and OR = 0.32, 95% CI = 0.10–1.03, respectively, when compared to subjects who had no GC therapy). The trend was still significant ($p = 0.01$) when subjects were classified by <2-, 2–6- and >6-month treatment period, even though based on small numbers. Subjects (18 cases and 26 controls) with a <2-month treatment had an OR = 0.44 (95% CI = 0.21–0.94); subjects who were treated for 2–6 months (3 cases and 4 controls) had an OR = 0.39 (95% CI = 0.07–2.16); and subjects (3 cases and 8 controls) with a >6-month treatment (range 6 months to 5 years) had an OR = 0.26 (95% CI = 0.05–1.32).

To evaluate whether the effect of glucocorticoids on melanoma risk could be affected by topical treatment for dermatologic diseases in comparison to treatment for more systemic health problems, we considered the reasons for GC treatment and route of administration. The reason for GC therapy did not appear to affect the odds ratio ($p = 0.25$). Compared to subjects who had no GC therapy, subjects (9 cases and 18 controls) who were treated with GC for dermatologic diseases (eczema, dermatitis and other skin diseases) had an OR = 0.28 (95% CI = 0.10–0.80), and subjects (16 cases and 21 controls) who were treated for other health conditions had an OR = 0.58 (95% CI = 0.26–1.28). Similarly, route of GC administration did not appear to significantly affect the association ($p = 0.41$). Subjects (7 cases and 12 controls) who had GC topically admin-

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*Correspondence to: Genetic Epidemiology Branch, National Cancer Institute/NIH, 6120 Executive Blvd. - EPS 7114, Bethesda, MD 20892-7236, USA. Fax: +301-402-4489. E-mail: landim@mail.nih.gov

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istered on their skin had an OR = 0.30 (95% CI = 0.08–1.01), while subjects (18 cases and 24 controls) who had GC through other administration routes had an OR = 0.53 (95% CI = 0.25–1.13) compared to subjects with no GC therapy.

Reasons for treatment and administration route were not significantly associated with length of treatment in control subjects ($p = 0.51$ and $p = 0.39$, respectively). No differences were found when analyses were repeated, excluding the hospital volunteers and trauma patients from the control group.

We considered potential sources for bias. Subjects under treatment with GC for skin-related diseases may have sought dermatologic examinations more frequently than others and consequently may have had suspicious moles removed more frequently, or earlier, than others. We adjusted the association between GC use and CMM risk for frequency of moles removed (in addition to age and gender and pigmentation characteristics) and found no substantial change in the risk estimate: 22 cases (4 GC users and 18 nonusers) and 20 controls (7 GC users and 13 nonusers) had a mole removed (OR = 0.41, 95% CI = 0.21–0.82). Subjects who had skin diseases may have spent less (or more) time in the sun. However, the odds ratios did not substantially change after adjustment for sun exposure (OR = 0.42, 95% CI = 0.22–0.82; OR = 0.40, 95% CI = 0.21–0.77 for sun exposure during vacation and occupation, respectively), UV lamp use (OR = 0.38, 95% CI = 0.20–0.74) or history of sunburns (OR = 0.39, 95% CI = 0.20–0.75). In fact, GC use was not associated with sun exposure ($p = 0.34$ and $p = 0.63$ for exposure due to vacation and due to occupation, respectively), UV lamp use ($p = 0.99$) or history of sunburns ($p = 0.40$) in control subjects. Finally, control subjects may have been more willing to participate in a study that involved skin examination if they had had a dermatologic problem, which could be treated with GC. We consider this unlikely, since inexpensive dermatologic examinations can be easily obtained at any public hospital in Italy, so a free examination for our study would not be a strong incentive for participation.

In conclusion, glucocorticoid-based therapy appeared to be protective against melanoma incidence in a case-control study in a Mediterranean population. The degree of protection increased with treatment duration and was not associated with reason for treatment or route of administration. Larger studies are needed to confirm this finding.

*Yours sincerely,*

Maria Teresa LANDI, Andrea BACCARELLI, Donato CALISTA, Thomas R. FEARS and Giorgio LANDI

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